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Related Application

This application is a continuation in part of copending application serial number 723,844 filed April 16, 1985, now abandoned.

~~BACKGROUND OF THE INVENTION~~

ABSTRACT OF THE DISCLOSURE

This invention is ~~concerned with~~ directed to compositions for nasal administration of a vitamin B_{12} to a human suffering a vitamin B_{12} deficiency. It is also directed to ~~concerned also with~~ such compositions in dosage unit form and with methods of administering such compositions.

BACKGROUND OF THE INVENTION

Cyanocobalamin is a vitamin B_{12}, and is one of the B_{12} class of vitamins which includes vitamin B_{12a} (hydroxocobalamin), vitamin B_{12b} (aquacobalamin), vitamin B_{12c} (nitrilocobalamin), coenzyme B_{12} (5'0deoxyadenosine cobalamine) and methyl B_{12} (methyl cobalamine). Cyanocobalamin is the principal member of the class, and the most widely employed in medicine. This invention will be described as it relates to cyanocobalamin, but those skilled in the art will recognize that the invention is aplicable to the class.

Vitamin B_{12} is an essential compound for normal growth, hematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. It was first isolated from liver concentrate by Rickes and his coworkers in 1948 and structurally elucidated by Hodgkin and her coworkers in the late 1950's. It is currently commercially available as a tablet and as an injectable.

Therapeutically, vitamin B_{12} is employed in the treatment of a variety of B_{12} deficiency afflictions, principally anemias such as pernicious and diplyllobothrium latum. Although the minimum daily requirement of vitamin B_{12} is approximately 0.1 ug, the generally prescribed initial therapeutic dose is 100 to 1000 ug given intramuscularly. Maintenance therapy with vitamin B_{12} is usually 100 ug intramuscularly, monthly and must be continued for life.

Since pernicious anemia is often a disease of later years when many sufferers have reduced muscle mass or are atrophic, repeated intramuscular injections of vitamin B_{12} can be inconvenient, painful and often require doctor's visits. In some cases at least in the early stages, hospitalization is required. As a result, there is a need for a more convenient, less painful and less expensive method of administering vitamin B_{12}, particularly one that would not require hospitalization or repeated physician contacts.

Unfortunately, up to the present time no efficient method of administering B_{12} which will achieve therapeutically useful blood levels of the vitamin except parenteral administration has been devised.

In 1953 and 1954 Monto et al in Am. J. Med. Sci., 223, 113 (1953) and Arch. of Int. Med. 93,219 (1954) described administration of B_{12} by nasal inhalation and instillation. The vehicles for administration were ~~aquerous~~ aqueous isotonic sodium chloride solution and lactose powder. Although the results were reported as effective, safe and economical, the fact is that parenteral administration remains the only method regarded by the medical community as a safe, reliable and effective method for treating vitamin B_{12} deficiencies in humans. No composition for nasal inhalation or instillation has become commercially

available for nasal administration to mammals. Neither have there been any further publications describing nasal inhalation or instillation of which applicant is aware.

The difficulty with nasal instillation by nasal dosage as the procedure is described in the cited articles is that most of the B_{12} passes immediately into the throat. It is not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B_{12} so administered is, in fact wasted.

Compositions have now been discovered for the nasal administration of B_{12} which can be kept in contact with the nasal mucosa for an extended period of time. During the time the compositions are in such contact, the B_{12} is uniformly absorbed from the compositions through the nasal mucosa and is then uniformly distributed systemically. The use of the compositions, because of the efficiency with which the B_{12} is absorbed allows the use much lesser amounts of B_{12} than is normally present in parenteral B_{12} compositions. Moreover, since the patient can self administer the B_{12}, the need for hospitalization or physician contacts is minimized and may even be eliminated.

THE INVENTION

This invention provides vitamin B_{12} containing compositions specifically formulated for nasal administration which will, unlike aqueous isotonic sodium chloride compositions, remain in contact with the nasal mucosa for a sufficiently long period of time to permit consistent, continuous and uniform absorption of therapeutically effective amounts of a vitamin B_{12} through the nasal mucous membrane.

The invention, therefore comprises compositions containing a therapeutically effective amount of a vitamin B_{12}, such compositions being sufficiently viscous to maintain themselves in the nasal passages for a period of time which is long enough so that most of the B_{12} is absorbed. The compositions are stable, easy to handle, and may be self administered by the patient.

More specifically the compositions of the invention are for nasal administration and contain a therapeutically effective amount of a vitamin B_{12} in an isotonic aqueous buffer at a pH of from about 4 to 6. The compositions may be in the form of gels, lotions, ointments, creams and the like and will contain a sufficient amount of a thickening agent so that the viscosity is from about 2500 to 6500 cps, although more viscous compositions even up to 10,000 cps may be employed. The preferred compositions have a viscosity of 2500 to 5000 cps, since above that range they become more difficult to administer.

Due to the efficiency with which the B_{12} is adsorbed from the compositions of this invention, a therapeutically effective amount of B_{12} for nasal administration will normally be appreciably less than for other methods of administration. Typically the concentration of B_{12} in a composition of the invention will be 0.05% to 1% by weight based on the total weight. In dosage unit forms the dosage will normally be from about 50 to 1000 micrograms.

The pH of the compositions of this invention is from about 4 to 6. At this pH, B_{12} is stable so that the compositions have a shelf life which may be a year or more. Additionally, at this pH, irritation of the nasal mucosa is minimal. The pH is maintained with a ~~physiuologically~~ physiologically acceptable buffer composition suitably an acetate, citrate, phosphate, phthalate, borate, or other buffer.

Acetate and citrate buffers are preferred for convenience and economy.

The isotonicity of the composition is accomplished using sodium chloride, or other pharmaceutically acceptable agent such as dextrose, boric acid, sodium tartrate or other inorganic or organic solute. Sodium chloride is preferred particularly for buffers containing sodium ions.

Viscosity of the compositions is maintained at the selected level using a therapeutically acceptable thickening agent. Methyl cellulose is preferred because it is easily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity.

Preferred compositions within the scope of this invention will contain a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of humectants can be employed including, for example sorbitol, propylene glycol or glycerol. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

An enhanced absorption of B_{12} across the mucous membrane can be accomplished employing a surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol. The usual concentration is from 1% to 10% based on the total weight.

A preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed. A suitable concentration of the preservative will be from 0.02% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The therapeutically effective compositions of this invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender, or other standard machine to produce a concentrated mixture which is then adjusted to the final concentration and viscosity by the addition of water.

A typical composition of this invention contains the following components per 100 ml.

Benzyl alcohol, NF	1.50ml
Sodium chloride, NSP	0.82gm
Methyl cellulose, USP (400 cps)	2.00gm
Acetic acid, NF	0.10gm
Sodium acetate (anhyd, USP)	0.27gm
Sorbitol soln., USP	5.00ml
Cyanocobalamine, USP	0.10gm
Water, purified	q.s. 100.00ml

The viscosity of the formulation is about 4500 cps. The pH is about 5.

The following non-limiting examples are given by way of illustration only and are not to be considered limitations of this invention of which many apparent variations are possible without departing from the spirit or scope thereof.

EXAMPLE 1

The following compositions prepared by mixing.

A

Phenylmercuric Acetate NF	⊂	0.002g
Boric Acid NF	⊂	1.740g
Methylcellulose (4000 CPS) USP	⊂	2.000g
Acetic Acid NF	⊂	0.100g
Sodium Acetate (Anhydrous) USP	⊂	0.270g
Glycerin USP	⊂	5.000ml
Cyanocobalamin USP	⊂	0.100g
Water, Purified USP	⊂ q.s.	100.000ml

B

Benzalkonium Chloride NF	⊂	0.020g
Potassium Chloride USP	⊂	1.080g
Hydroxyethyl Cellulose (3500-4000 CPS) NF	⊂	1.000g
Acetic Acid NF	⊂	0.100g
Sodium Acetate (~~Anhydrivs~~ Anhydrous) USQ	⊂	0.270g
Propylene Glocol USP	⊂	5.000ml
Cyanocobalamin USP	⊂	1.000g
Water, Purified USP	⊂ q.s.	100.000ml

C

Thimerosal USP	⊂	0.002g
Dextrose USP	⊂	5.120g
Polysorbate 80 USP	⊂	10.000g
Methylcellulose (4000 CPS) USP	⊂	1.33g
Acetic Acid NF	⊂	0.100g
Sodium Acetate (Anhydrous) USP	⊂	0.270g

Glycerin USP		5.000ml
Cyanocobalamin USP		0.500ml
Water, Purified	q.s.	100.000ml

D

Methylparaben NF		0.020g
Propylparaben NF		0.010g
Sodium Chloride USP		0.820g
Xanthan Gum NF		2.000g
Acetic Acid NF		0.100g
Sodium Acetate (Anhydrous) USP		0.270g
Propylene Glycol USP		5.000g
Cyanocobalamin USP		0.200g
Water, Purified	q.s.	100.000ml

The viscosities of the compositions are within the range defined above.

The typical composition disclosed above just prior to the examples was tested in humans in order to determine quantitative increases in B_{12} Blood Levels following nasal administration. Three normal volunteers received 0.1cc of the cited composition (100ug B_{12}) inserted nasally with a nasal syringe applicator. Serial Blood Samples were drawn from the subjects at 0, 0.05, 0.08, 0.16, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24 hours following dosing and assayed for B_{12} content by radioimmunoassay.

It was found that in less than 15 minutes after administration the serum level of B_{12} was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

The actual plasma blood levels of B_{12}, in the subjects following its nasal administration in the above cited composition, were:

TIME (hours)	PLASMA LEVELS (Picograms)
0	599
0.05	631
0.08	628
0.16	674
0.25	754
0.5	729
1.0	804
2.0	794
3.0	769
4.0	727
6.0	752
8.0	803
24.0	729

An additional and similar study was performed with three human subjects using the same composition in which 0.2cc was administered intranasally (200ug B_{12}). The actual plasma blood levels obtained were:

TIME (hours)	PLASMA LEVELS (Picograms)
0.0	591
0.05	630
0.08	637
0.16	680
0.25	699
0.5	742
1.0	809
2.0	849

3.0	786
4.0	764
6.0	722
8.0	742
24.0	675

EXAMPLE 2

A composition of this invention containing the following components per 100 ml was prepared.

TIME (hours)	PLASMA LEVELS (Picograms)
0.0	731
0.05	734
0.08	725
0.16	845
0.25	837
0.5	940
1.0	975
2.0	1027
3.0	1038
4.0	1002
6.0	969
8.0	945
24.0	925

Again it was found that in approximately 15 minutes after administration the serum level of B_{12} was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

EXAMPLE 3

The following comparative experiment was conducted on forty normal, human, adult volunteers to compare the availability, speed of availability, and duration of availability of B_{12} administered by various routes. Commercially available oral and ~~bilingual~~ sublingual tablets were compared with the compositions of this invention which were administered orally. All samples were tested by high performance liquid chromatography for B_{12} per dosage unit was as follows:

Methyl Cellulose	20gm
Sodium Citrate	3.2gm
Citric Acid	1.2gm
~~Benzalkonium~~ Benzalkonium chloride 50%	0.4ml
Cyanocolalamine	2.5gm
Purified Water q.s. to	100ml

The composition used to prepare the 400 mcg ~~intrumural~~ intranasal dosage unit was identical except that it contained 4.0 gm. of cyanocolalamine.

Serial blood samples were from the subjects at 0, 5, 1, 2, 4, 8, 24, 48 and 72 hours following dosing and assayed for B_{12} content by radioimmunoassay.

The results are shown in Figures 1, 2, 3 and 4 in which concentration in picograms per ml. is plotted against time. The results are also summarized in table 1. In the table, the Baseline is the B_{12} average concentration of B_{12} in the volunteer group prior to B_{12} administration.

From an analysis of the figures and the tables, the following unexpected advantages for nasal administration of B_{12} in the compositions of this invention will be apparent:

1. Increased blood levels at lower dosages.

2. Maximum blood levels achieved more rapidly, and at lower dosage levels.

3. High blood levels maintained for entire period of test as indicated by larger areas under the carve.

4. Substantially higher blood levels at lower dosages even two days after administration.

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TABLE 1

A COMPARISON OF THE BIOAVAILABILITY OF VITAMIN B_{12} FOLLOWING INTRANASAL, ORAL, AND SUBLINGUAL ADMINISTRATION IN NORMAL SUBJECTS

Number of Subjects	Vitamin B_{12} Treatment	Average Baseline pc/ml	Average Maximum Increase in Plasma B_{12} Concentration	Average time to Reach Maximum B_{12} Plasma Concentration	Average Area Under The Curve (pcg hr/ml)	Average Increase In Plasma B_{12} Concentration in 48 hrs. (pcg/ml)
10	500mcg Oral Tablet	665.8	233.51 pcg/ml	25.60 Hours	9,503	92.6
10	500 mcg Sublingual Tablet	599.8	196.64 pcg/ml	5.70 Hours	6,010	51.1
10	250mcg Intranasal	577.2	1167.31 pcg/ml	2.5 Hours	24,266	193.5
10	400mcg	472.1	1967.98 pcg/ml	1.61 Hours*	28,690	178.9

* A 24:00 hour data point was considered and outlier and eliminated from the calculation of the average.

CY What is claimed is: